Effectiveness of Cryotherapy on Function, Pain Intensity, Swelling, Dorsiflexion Range of Motion in Acute Ankle Sprain: Protocol for the Frost Randomised Controlled Trial

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Abstract

**Background:** Cryotherapy is a low-cost treatment option recommended by clinical practice guidelines in acute ankle sprain. However, current quality of the evidence that supports cryotherapy is still unclear. New high-quality randomised controlled trials are needed. The aim of the FROST randomized controlled trial is to investigate the effectiveness of cryotherapy on function, pain intensity, swelling and dorsiflexion range of motion in people with an acute episode of ankle sprain.

**Methods:** This is a protocol of the FROST two-arm randomised controlled trial. Eighty-two participants over 18 years old presenting grade I or II ankle sprain up to 72 hours from the episode will be randomly allocated to Ice Group (i.e., home prescription to apply cryotherapy on the injured ankle with elevation plus non-steroidal anti-inflammatory medication – NSAID) or No Ice Group (i.e., elevation plus NSAID). Our primary outcome is function measured by the Lower Extremity Functional Scale (LEFS) questionnaire. Our secondary outcomes are pain intensity (11-points numerical rating scale), swelling (figure-of-eight method) and dorsiflexion range of motion (goniometry). Participants will be assessed at baseline, post-treatment (7 to 14 days) and 12 weeks after allocation. Analysis will follow the intention-to-treat principle using mixed linear models.

**Discussion:** The results of this study will clarify the effectiveness of cryotherapy in acute ankle sprain for better clinical decision-making processes.

**Trial registration (2a):** REBEC, ID RBR-8v9gr9c - Effectiveness of Cryotherapy on function, pain intensity, swelling, dorsiflexion range of motion in Acute Ankle Sprain: a randomized controlled trial - the FROST study – registered 02 mar. 2023 - [https://ensaiosclinicos.gov.br/rg/RBR-8v9gr9c](https://ensaiosclinicos.gov.br/rg/RBR-8v9gr9c)

**INTRODUCTION (6a, 6b)**

Ankle sprain is a common health condition with a period prevalence of 12% in the general population and seven sprains per 1000 exposures in athletes [1]. After a new episode of ankle sprain, its related disability and potential chronic ankle instability or recurrence bring direct (e.g., expenditures with health professionals) and indirect (e.g., productivity loss) costs [2]. Thus, effective therapies are important in the decision-making processes for acute ankle sprain. Treatment options frequently used after an ankle sprain comprise non-steroidal anti-inflammatory medication (NSAIDs) [3], cryotherapy [4, 5], surgical treatment [6], joint mobilization [7], kinesiotherapy [8, 9], braces [10], acupuncture [11], among others.

Cryotherapy is a low-cost and easy-to-use treatment that has been recommended by clinical practice guidelines after a new episode of ankle sprains [5, 11]. Plausibility for cryotherapy remains on inflammation control [12,13], in addition to local analgesia by decreasing nociceptive conduction [14]. Although preliminary basic research formulated hypotheses to be tested in clinical trials and to understand mechanisms of action, we advocate that clinical choices should be based on the high-quality clinical research that investigates clinical outcomes meaningful to patients (e.g., function and pain...
intensity) and avoid the use of surrogate outcome measures [15]. At the moment, evidence from clinical research is still unclear [16].

A previous systematic review [16] that investigated the effectiveness of cryotherapy in acute ankle sprain showed lack of clinical research to support the therapy, raising the importance of new high-quality randomised controlled trials to investigate whether cryotherapy enhances the effects of other effective intervention (e.g., NSAIDs). Therefore, the aim of the FROST trial is to investigate whether cryotherapy enhances effects of NSAIDs on function, pain intensity, swelling and dorsiflexion range of motion in people with an acute episode of ankle sprain. This randomised controlled trial may play an important role as part of an informed decision-making process.

**STUDY OBJECTIVES (7)**

The primary aim of this trial is to investigate whether cryotherapy enhances effects of NSAIDs, limb elevation and rest on function in people with acute ankle sprain. The secondary aim is to investigate whether cryotherapy enhances effects of NSAIDs, limb elevation and rest on pain intensity, swelling and dorsiflexion range of motion in people with acute ankle sprain.

**METHODS**

**Elaboration of the protocol**

This protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline [17] (Additional File 1). and the results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement when the study is completed [18].

**Study design (8)**

This is a prospective, parallel group, two-arm, superiority randomised controlled trial with 1:1 allocation ratio.

**Settings and eligibility criteria (9, 10)**

Study participants will be people aged 18 to 60 years old seeking care for a new episode of acute ankle sprain at the emergency service of the Nossa Senhora da Saúde Hospital, in Diamantina, Brazil.

The inclusion criteria will be:

- People aged from 18 to 60 years old;
- Clinical diagnosis of grade I or II ankle sprains by a trained clinician, suggesting an incomplete ligament rupture [19];
- Duration up to 72 hours from the new episode of ankle sprain to the day of the medical appointment;
- Bone fractures excluded by the Ottawa ankle rules and radiography [20].
The exclusion criteria will be as follows:

- Grade III (severe) ankle sprain, suggesting complete ligament injury, determined by a clear positive test of the anterior drawer and/or inversion stress test, accompanied by severe swelling, haemorrhage, high level of pain on palpation, in addition to total loss of the ability to support weight on the foot and of the dorsiflexion range of motion [19].
- Open injuries that contraindicate the application of ice (e.g., any degree of vascular ulcer);
- Application of any cryotherapy more than once since the episode, before the allocation process;
- Application of any cryotherapy after being assigned to control group;
- Any condition that contraindicate the application of ice (e.g., Raynaud's syndrome), or any other intervention prescribed in the trial.

**Intervention {11a, 11b, 11c, 11d}**

The intervention will be reported according to the Template for Intervention Description and Replication (TIDieR) checklist and guide [21] (Additional File 2).

**Ice Group {22}**

Participants allocated to the ‘Ice Group’ will receive home prescription to submerge the ankle on a bucket of ice and water until cover the area of swelling and pain, sitting with 90° knee flexion in the affected limb, for up to three times per day, for 20 minutes, during seven days. In addition to cryotherapy, ankle elevation above the chest level, NSAID (i.e., nimesulide 100 mg, 2 times a day, during 5 days) and medical advice to rest for three days are prescribed [22, 12]. Daily phone calls and/or text messages by physiotherapists motivate record of applications using an intervention diary to assess adherence and adverse effects (Additional file 3). When participants do not adhere to immersion, alternative ice packs are prescribed in the same dosage.

Evidence from basic research suggests that cryotherapy may act to reduce pain intensity, inflammation and swelling, leading to improvement on ankle function. In pain, cryotherapy can decrease nerve conduction velocity, decreasing muscle spasms generated by spinal reflex after trauma [23], in addition to stimulating thermoreceptors that could inhibit the processing of nociception signals by the central nervous system, increasing the pain threshold [14]. By decreasing the local temperature, cryotherapy can reduce the metabolic demand of the area, avoiding the formation of swelling and the risk of a secondary injury caused by post-traumatic hypoxia and consequently preventing cell death [24]. Other mechanisms that can contribute to the reduction of swelling are local vasoconstriction, which leads to a decrease in blood flow to the tissue and a decrease in vascular permeability [25, 26].

**No Ice Group**

Participants allocated to the ‘No Ice Group’ will receive the same interventions of the ‘Ice group’ but with no ice. The prescription will be consisted of ankle elevation above the chest level, NSAID (i.e., nimesulide
100 mg, 2 times a day, during 5 days) and medical advice to rest for three days. Daily phone calls and/or text messages will also motivate record of applications in the ‘No Ice Group’.

Patients will be advised to not be part of any rehabilitation program until the end of the trial (i.e., 12 weeks after allocation). In case of non-compliance with this orientation, we will perform sensitivity analysis to minimise the concomitant care effects. Adverse effects have rarely been reported in the literature. In case of superficial skin burn, itching and cold-induced peroneal nerve palsy or any adverse symptoms that may be related to the interventions in this study, the patient will be instructed by the physiotherapist to discontinue their assigned interventions. They will be analysed normally according to their allocation in all segments and will be reported as an adverse event.

**Outcome measures**

*Primary outcomes*

The primary outcome will be function, measured with the 0-80 Lower Extremity Functional Scale (LEFS) questionnaire, with higher scores meaning better functional status, and a Minimum Clinically Important Difference (MCID) of 9 points [27].

*Secondary outcomes*

The average pain intensity in the last 24 hours, measured with an 11-point Numerical Rating Scale (NRS), with higher scores meaning worse pain intensity [28] and MCID of 1.3 points [29];

Swelling, measured using the figure-of-eight method, which consists of circumference using a tape measure of the areas with the highest concentration of ankle swelling (the region of the anterior talofibular, calcaneofibular and anterior tibiofibular ligaments). The measurement is made by positioning the starting point (0) of the tape measure over the midpoint between the articular projection of the tibialis anterior tendon and the lateral malleolus, directing the tape to the centre of the medial longitudinal arch of the foot, over the navicular bone, passing through the base of the fifth metatarsal and crossing the upper face of the midfoot towards the lower point of the medial malleolus, passing through the calcaneal tendon, lower point of the lateral malleolus, until finding the zero point of the measure tape [30]. The Minimum Detectable Change (MDC) is 0.96 centimetres (cm) [31];

Dorsiflexion range of motion, assessed by two measurements of active ankle goniometry with the patient in the prone position (knee extension and with 90° of knee flexion to reduce the influence of the gastrocnemius). The ankle will be positioned in a position of 0° of movement in the sagittal plane, placing the goniometer axis over the calcaneus, with the fixed arm aligned with the calcaneal tendon and the mobile arm aligned with the second metatarsal. A digital goniometer will be used as measurement tool. The participant will be instructed to perform as much dorsiflexion as possible [32, 33, 34]. The MDC for this measurement is 6 degrees (°) [32].
Assessors were trained to perform the dorsiexion range of motion goniometry and the figure-of-eight technique followed by a pilot study for intra- and inter-examiner reliability. Data for the Intra-class Correlation Coefficient (ICC) and its 95% confidence interval (95%CI) were collected on two different measurement occasions, with an interval of 1 week. We recruited six individuals of both sexes (three males and three females), collecting measurements from both lower limbs (n =12). We found a ICC of 0.95 (95% CI 0.80 to 0.98) for intra-examiner and 0.93 (95% CI 0.83 to 0.98) for inter-examiner reliability for goniometry. For the figure-of-eight technique, a ICC of 0.97 (95% CI 0.84 to 0.99) for intra-examiner and 0.96 (95%CI 0.88 to 0.99) was found.

**Procedures and participant timeline** \(^{13, 26a}\)

All eligible participants will be informed about the study and must sign the consent form provided by the physicians prior to participation (Additional File 4). Baseline assessment will include age, Body Mass Index (BMI), sex, dominant limb, history of previous ankle sprains, ability to bear weight on the affected ankle (Yes/No), comorbidities. The degree of injury will be classified according to the Birrer et al. (1999) \(^{19}\) classification. The outcomes of interest (function, pain intensity, swelling and dorsiexion range of motion) will be collected at the baseline and reassessed at the following time-points: Short term (i.e., 7 to 14 days after allocation), and long-term (i.e. 12 weeks after allocation). Furthermore, we will investigate the immediate effects of cryotherapy on pain intensity in a time-point between 24h to 48h after baseline. A schematic diagram is available in Figure 1.

![Figure 1 – Schematic diagram of the procedures and participant timeline. t₁ – Baseline assessment; t₂ – 24-48 assessment (immediate effects); t₃ – 7-14 days’ assessment (short-term; t₄ – 12 weeks’ assessment (long-term).](image)

**Data analysis**

**Sample calculation** \(^{14}\)

**Function (LEFS) – primary outcome**

The sample calculation was performed considering the MCID value of 9 points for the measurement of the primary outcome \(^{27}\), and a standard deviation of ±12.85 based on a previous study \(^{4}\). A sample of 82 participants (41 per group) is necessary for a minimum detection of the effect size, taking into account a statistical power of 80%, \(\alpha\) of 5% and a dropout rate of 20%.

**Pain Intensity (0-10 NRS) – secondary outcome**

The sample calculation was performed considering the MCID value of 1.3 points \(^{29}\), and a standard deviation of ±0.8 based on a previous study \(^{35}\). A sample of 16 participants (8 per group) is necessary for a minimum detection of the effect size, taking into account a statistical power of 80%, \(\alpha\) of 5% and a dropout rate of 20%.
Swelling (figure-of-eight method) - secondary outcome

The sample calculation was performed considering a difference of 3.4 cm and a standard deviation of ±3.8 based on a previous study [31]. A sample of 50 participants (25 per group) is necessary for a minimum detection of the effect size, taking into account a statistical power of 80%, α of 5% and a dropout rate of 20%.

Dorsiflexion range of motion (Goniometry) - secondary outcome

The sample calculation was performed considering a difference of 6° and a standard deviation of ±6.8 based on a previous study [35]. A sample of 52 participants (26 per group) is necessary for a minimum detection of the effect size, taking into account a statistical power of 80%, α of 5% and a dropout rate of 20%.

Recruitment (15)

Eligible people seeking care for acute ankle sprain at the emergency of the Nossa Senhora da Saúde Hospital will be referred to researchers who will contact them to check eligibility, explain the trial and ask for formal consent. To inform the population about the ongoing trial, social media and posters will be used.

Randomisation and allocation (16a, 16b, 16c)

The randomisation sequence for the experimental and control groups, with a 1:1 allocation ratio, will be computer-generated by one of the researchers who will not be involved in recruiting and assignment. The sequence will be generated in blocks of 4, 6 and 8, in random order. Doctors working in the emergency department will enrol and assign participants to the groups. The allocation will be hidden in sequentially numbered opaque sealed envelopes. All procedure will be conducted following recommended methods [36].

Blinding (17a, 17b)

The statistician will be blinded to the allocation of the participants. The data will be encoded in an unidentifiable way and will not contain any information that can raise suspicions about the allocation of the participants. Additionally, the assessors will be blinded for the secondary outcomes (i.e., figure-of-eight method and goniometry). The circumstances in which unblinding is allowed will be if the application of ice or any of the interventions applied in this study generate serious side effects or damage that requires medical assistance.

Analysis of treatment effects (20a, 20b)

The statistical analysis will be performed following the intention-to-treat principle. The normality of the data will be tested using the Kolmogorov-Smirnov test and the homoscedasticity of the data will be tested using the Levene test. Parametric data will be expressed as means and standard deviation and
analysed with Mixed-Effects Models for repeated measures considering group versus time interaction and treatment effects adjusted for baseline values and a post-hoc Bonferroni analysis. In cases of non-parametric data, median and its upper and lower limits will be expressed, and analysed using the Generalized linear mixed effects models. All statistical analyses will be performed using the Stata software version 17.0 (StataCorp LLC, College Station, United States). The effect sizes will be interpreted based on MCIDs of our outcomes of interest. There are no subgroup analyses planned.

DISCUSSION

Implementation and study group

The project will involve emergency departments in Diamantina, Brazil. People who suffer from acute ankle sprains who seek emergency services will be invited, and if they are interested in participating in the study, they will pass the eligibility criteria.

Planning for supervision and monitoring {14, 21a}

The study will be conducted and monitored by the principal investigator (JPM) under the supervision of the co-author (VCO), with the assistance of the research team. All ethical principles as provided by the Declaration of Helsinki will be followed by all members of this research throughout the study. A data monitoring committee will not be necessary since this is a short duration trial with minimal risks.

Interim analyses {21b}

There are no interim analyses.

Plan for data integrity and management {5c, 19, 27, 29}

All study-related information will be stored securely in locked file cabinets in areas with limited access at the university. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. Participants’ study information will not be released outside of the study without the written permission.

Data will be entered in Microsoft Excel. The research data will be monitored weekly by examining the data entered. Any errors in the entry will be identified (if any) by data double entry and corrected. The consent forms will be digitized and stored on password-protected computers of the lead researcher and at the University, along with other research data files. In addition, we will upload the files in online spreadsheets to the research group lead researcher (VCO) and first author (JPM) account. Only VCO, GMF, SSBFS, RCF and VGO will have access to the full dataset during the study, and JPM will have access at the end.

Imputation Procedure for Missing Data {20c}
To handle missing data, we will classify as Missing Not at Random (MNAR) when dropouts are due to lack of efficacy and adverse effects, and Missing Completely at Random (MCAR) when the loss of follow-up does not depend on observed or unobserved measurements (e.g. patient moving to another city for non-health reasons). We are planning to perform Mixed-effect models for repeated measures (MMRM) to handle missing data due to MCAR, and single imputation methods (such as best or worst case imputation, i.e., assigning the worst possible value of the outcome to dropouts for a negative reason (treatment failure) and the best possible value to positive dropouts (cures)) when we consider missing as MNAR. We are planning sensitivity analyses to evaluate if the methods used to handle missing data produce any important difference on the findings [37].

**Retention (18b)**

Strategies to reduce attrition and maximize data collection completeness will include: daily contact with participants through phone calls and messages; appointment scheduling at the time of enrollment; and retention monitoring. The reasons for the withdrawal will be collected.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<td>ICC</td>
<td>Intra-class Correlation Coefficient</td>
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<tr>
<td>LEFS</td>
<td>Lower Extremity Functional Scale</td>
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<tr>
<td>MCAR</td>
<td>Missing Completely At Random</td>
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<tr>
<td>MCID</td>
<td>Minimum Clinically Important Difference</td>
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<td>MDC</td>
<td>Minimal Detectable Change</td>
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<td>MMRM</td>
<td>Mixed-Effect Models For Repeated Measures</td>
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<tr>
<td>MNAR</td>
<td>Missing Not At Random</td>
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<td>NRS</td>
<td>Numerical Rating Scale</td>
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<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<td>REBEC</td>
<td>Registro Brasileiro de Ensaios Clínicos</td>
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<tr>
<td>SPIRIT</td>
<td>Standard Protocol Items: Recommendations for Interventional Trials</td>
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**Declarations**

**Ethical approval and consent to participate**
Written informed consent will be obtained from participants for publication and any accompanying images. This study was approved by the Research Ethics Committee of the Federal University of Vales do Jequitinhonha and Mucuri (UFVJM) (CAAE: 58542222.2.0000.5108) (Additional File 5).

**Conflict of interests (28)**

The authors declare no conflict of interest.

**Financing (4)**

Not applicable.

**Acknowledgement**

We thank the Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM) for institutional support and the CNPq, CAPES (Finance Code 001), and FAPEMIG for support and scholarships.

**Authors' contributions (5a, 31b)**

Conceptualization and project management: JPM, VCO; Writing: JPM, VCO; Data Collection: GMC, FSA, AJS, IML, and SPS will collect characteristics and baseline results data and JPM will be the examiner of post-intervention outcomes and follow-ups; Recruitment and Assignment: GMC, FSA, AJS, IML and SPS; Intervention: GMC, FSA, AJS, IML and SPS will prescribe the intervention, and FGC and HJS will be the physiotherapists responsible for calls and text messages; Analysis: HJS will be the statistician and will generate the random sequence; Data integrity and management: VCO, GMF, SSBFS, RCF and VGO. We have no intention to hire professional writers.

**Data sharing statement (31c)**

Unidentified data set that will support the findings of this study will be available from the corresponding author, on reasonable request, for transparency and reproducibility purposes.

**Ethics and disclosure (22, 30, 31a)**

The study was approved by the UFVJM Ethics Committee. Standard informed written consent will be obtained from each participant. The study was previously registered on the Registro Brasileiro de Ensaios Clínicos (REBEC) website: www.ensaiosclinicos.gov.br (ID RBR-8v9gr9c). The findings will be published in international journals and presented at national and international conferences. The results will be disseminated regardless of the magnitude or direction of effect.

In case of adverse effects, the volunteers will be instructed to discontinue the treatment immediately, and will be referred for a new consultation with the doctors of the team linked to the project, as would happen outside the context of this research, since the use of cryotherapy in the management of acute ankle sprain is widely used in the institution's daily clinical practice. If clinically important favourable effects are
found in favour of the application of cryotherapy, patients in the comparator group (Group without ice) will be invited to receive treatment at the school clinic, in the physiotherapy department – UFVJM.

**Administrative information**

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers [17]. The order of the items has been modified to group similar items.

**Trial Status**

Protocol version 2 - 2023-Mar-05 (see Revision Chronology Table); Date of the first enrolment: 03/03/2023; Approximate date when recruitment will be completed: 03/03/2025.

**References**


Figures
<table>
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<td>$t_3$ Short-term (7-14 days)</td>
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**Figure 1**

Schematic diagram of the procedures and participant timeline. $t_1$ – Baseline assessment; $t_2$ – 24-48 assessment (immediate effects); $t_3$ – 7-14 days’ assessment (short-term; $t_4$ – 12 weeks’ assessment (long-term).
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1SpiritGuideline.docx
- AdditionalFile2TIDIERchecklist.docx
- AdditionalFile3InterventionDiary.docx
- AdditionalFile4ConsentForm.docx
- AdditionalFile6WHOdatalset.docx